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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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09/884,456

06/18/2001

Michael Houghton

223002010005

1937

7590

04/12/2005

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EXAMINER

MOORE, WILLIAM W

ART UNIT

PAPER NUMBER

1652

DATE MAILED: 04/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/884,456

Applicant(s)

HOUGHTON ET AL.

Examiner

William W. Moore

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 January 2005.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 27-44 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 27-44 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

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DETAILED ACTION

Priority and Declaration of Tatsuo Miyamura

Applicant's amendment to page 1, line 9 of the specification filed 10 January 2005 provides a chain of priority bringing the application into compliance with conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120. Applicant's provision of a copy of the Declaration under 37 CFR 1.132 of Tatsuo Miyamura filed in the related Reexamination application Control No. 90/005,512 overcomes the prior art rejection of record of claims herein.

Specification

Compliance with 37 CFR § 1.821 is required in response to this Office action. The specification, including the Description of the Drawing Figures, lacks designations that describe the disclosed nucleic acid sequences and amino acid sequences according to the requirements of 37 CFR § 1.821 for a Sequence Disclosure. While appropriate references to specific amino acid sequences are set forth in the claims with the format, "SEQ ID NO:n", where "n" is an integer corresponding to a sequence in the Sequence Disclosure, each recitation of a nucleotide or amino acid sequence embedded in the text of the specification, and each of the drawing descriptions of Figures 2-8 and 10 at page 3 of the specification, must also include references in the format, "SEQ ID NO:n", where "n" is an integer corresponding to a sequence in the Sequence Disclosure. See 37 CFR §§ 1.821(b), (c) and (d).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

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Claims 27-31 remain rejected under 35 U.S.C. 101 for the reasons set forth at page 3 of the communication mailed 09 July 2004 because the claimed invention is directed to non-statutory subject matter.

Applicant's arguments filed 10 January 2005 have been fully considered but they are not persuasive. Applicant argues that, when isolated or purified, a polynucleotide encoding a naturally-occurring gene is patentable subject matter, but the claims instead describe a **composition comprising** a polynucleotide that is indistinguishable from the RNA genome of the hepatitis C virus which, as the specification discloses, encodes a proteolytic polypeptide comprising an NS3 domain protease. No weight can be given to the term "isolated" in construing claims to compositions comprising this polynucleotide and the hepatitis C virus genome encodes polypeptides comprising each of the amino acid sequences recited by claims 27-31. Because claim 27 is stated in the disjunctive, polynucleotides encoding NS3 domain protease truncation analogs cannot remove the claimed subject matter from a description of a product of Nature: an isolated hepatitis C virus particle which is a composition of matter meeting the limitations of claims 27-31 and the basis for the prior art rejections sustained hereinbelow. The rejection of record is therefore sustained.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

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Claims 27-43 remain rejected, and the new claim 44 is now rejected, under the judicially created doctrine of obviousness-type double patenting for the reasons set forth at page 4 of the communication mailed 09 July 2004 as being unpatentable over claims 1-14 of U.S. Patent No. 5,371,017. While Applicant states that a terminal disclaimer will be field upon indication of allowable subject matter, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

The following is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim 36 remains provisionally rejected under the judicially created doctrine of obviousness-type double patenting for the reasons set forth at page 4 of the communication mailed 09 July 2004 as being unpatentable over claim 15 of copending Application No. 10/438,313, which is an application for reissue of U.S. Patent No. 5,371,017. While Applicant states that a terminal disclaimer will be field upon indication of allowable subject matter, the rejection must be maintained until and unless an effective terminal disclaimer is filed.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-44 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicant's arguments in the Response filed 10 January 2005 have been fully considered but they are not persuasive and are the occasion for this new ground of rejection of all pending claims where structural characteristics of Applicant's expression constructs that Applicant argues can account for proteolysis by the encoded products, while necessary for HCV-specific proteolysis, have been shown to be insufficient for HCV-specific proteolysis. Applicant argues at pages 9-12 of the Response that pages 3-6 and 8 of the specification, which point to a specific section in the NS3 domain as the

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key to proteolytic activity, constitute an adequate written description of a "NS3 domain hepatitis C virus protease or active . . . truncation analog" that is encoded by isolated polynucleotides, and maintained in the sequences of expression vectors, of claims 27-44 herein. Applicant suggests that pages 7-8 of the specification adequately describe an "active" truncation analog. Yet the specification states, at page 7, lines 19-21, that the proposed termini of the NS3 domain are "putative, the actual termini being defined by **expression and processing in an appropriate host** of a DNA construct **encoding the entire NS3 domain**" [emphasis supplied]. Applicant next suggests that teachings at pages 5-6 of the specification that a generic protease or analog can be defined by "analogy" with the amino acid sequence of the NS3 domain of a flavivirus, Yellow Fever Virus, might also give an adequate written description. These arguments are unpersuasive because the specification does not disclose identifying characteristics of the structure of a HCV protease that might be determined by "analogy" where there is no disclosure of either the expression of a DNA construct encoding the entire NS3 domain or the expression of any portion of the HCV polyprotein in a host cell appropriate for proteolytic processing of, at least, the NS3 domain. The specification provides no written description indicating that Applicant possessed a polynucleotide or expression vector of claims 27-44 encoding a protease that cleaves an HCV polyprotein at the time the instant disclosure was first filed where the specification (1) cannot define a NS3 domain, (2) cannot show whether components sufficient for the activity of a HCV protease are beyond the undefined NS3 domain or entirely within the undefined NS3 domain, and (3) does not disclose necessary components beyond an undefined NS3 domain permitting an HCV protease to conduct *cis* (intramolecular) cleavages of HCV.

Applicant's ultimate argument is that Example 5 of the specification is evidence of an activity, cleavage of the HVC polyprotein, constituting a functional definition of a

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protease. Thus the definition at page 6, lines 22-24, of the specification, "an enzyme derived from HCV which exhibits proteolytic activity . . . encoded in the NS3 domain of the HCV genome", is the proper basis for analysis of the presence or absence of an adequate written description of a polynucleotide or expression vector of claims 27-44. Applicant's Response specifically points to the report Example 5 of (i) cleavage of an 844-amino acid polypeptide expressed using the P600 construct into three fragments, (ii) cleavage of a 644-amino acid polypeptide expressed using the P500 construct into two fragments, (iii) cleavage of a 450-amino acid polypeptide expressed with the P300 construct into two fragments, and (iv) an absence of cleavage of a 350-amino acid polypeptide expressed using the P190 construct. Applicant alleges that these reported cleavages show HCV-specific, rather than *E. coli* host-specific, proteolysis.

The specification provides no depiction of these cleavages, discloses no *in vitro* cleavage of any polypeptide substrate by an isolated HCV protease, discloses no *in vitro* cleavage of a peptide substrate having amino acid sequences present in a HCV polyprotein, and discloses no isolation of a protease, whether a serine protease or a metalloprotease, from an *E. coli* host cell or another kind of host cell, that can cleave an integral HCV polyprotein or an HCV polyprotein segment *in vitro*. Indeed, the state of the art evidenced by the prior art of record does not exclude, and the specification does not eliminate, the likelihood that Applicant's recombinant expression in *E. coli* host cells of fusion polypeptides encoded by the P600, P500, P300 and P190 constructs of Example 4 comprising a 151-amino acid sequence region of human superoxide dismutase fused to the amino terminus of amino acid sequence regions of the HCV polyprotein, see, e.g., Figure 10, resulted in accumulation of the expressed products in inclusion bodies. The specification's hypothetical Example 6 addresses such misfolding and inactivation of foreign proteins recombinantly expressed in *E. coli* because it was an

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art-recognized problem at the time Applicant's priority document was filed. See also, Cousens et al., US 5,523,215, made of record herewith. It is not clear that any region of the HCV polyprotein in the P600, P500, or P300 fusion polypeptides Applicant had expressed in *E. coli* cells functions as a serine protease within these host cells and the subsequent art of record¹ herein fails to show that any HCV protease is active in *E. coli* host cells by, e.g., identifying amino- or carboxyl-terminal peptide sequences resulting from *in vivo* cleavage of an HCV polyprotein at art-recognized HCV protease cleavage sites. As discussed below, the disclosure of the specification indicates that the other source of art-recognized HCV-specific proteolytic activity, a metalloproteinase extending from the NS2 domain into the NS3 domain, cannot have been the source of cleavages reported in the specification for the P600, P500, or P300-encoded fusion polypeptides.

Applicant maintains that the specification need only show a *cis* (intramolecular) cleavage of some portion of the HCV polyprotein to meet the statutory requirement for an adequate written description and suggests that the Abstract, discussions at pages 8149 and 8155, and discussions accompanying Fig. 7 at page 8152 of Lin et al., 1994, of record, support the existence of a HCV protease-specific proteolytic activity in the NS3 domain portions of the P600, P500, and P300 fusion constructs. But the teachings of *cis* cleavages in publications cited by Lin et al., and in the work shown in Fig. 7 of Lin et al. make it clear that the art recognizes only two sites in the HCV polyprotein where *cis* cleavage occurs – the NS2/NS3 site and the NS3/NS4 site – and that a segment of

¹ Differing substantially from the hypothetical Example 6 of the specification, Sardana et al., 1999, made of record herewith, report the recovery from the **soluble** supernatant of an *E. coli* host cell lysate of a truncated NS3 domain protease component having the sequence of amino acids from position 1027 through position 1206 of the HCV_{BK} polyprotein. This is less extensive than the HCV1 NS3 region in the product encoded by Applicant's P300 construct but more extensive than the HCV1 NS3 region in Applicant's P190-encoded product. Sardana et al. expressed their NS3 protease component, which was not part of a fusion polypeptide, at low temperature (25°C) for only two hours in the host cells to ensure that it would be present in the soluble fraction of the host cell lysate, and assayed for HCV protease activity only in the presence of the NS4A peptide cofactor, a region absent from all polypeptides encoded by Applicant's four constructs discussed in Examples 4 and 5 of the instant specification.

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the HCV polyprotein having a sequence extensive enough to encompass both of these sites must be expressed in an active form in order to accomplish the *cis* cleavages. Lin et al. show, in Fig. 7A, that the characteristic 70kD product liberated in successive *cis* cleavages when the entire 3011-amino acid polyprotein was its self-substrate. Within the HCV polyprotein, the NS4A cofactor region is adjacent to the NS3 domain, thus can sustain the NS3/NS4 cleavage, just as the entire sequence of the NS2 metalloprotease domain bordering the NS3 domain is present in the polyprotein and available to sustain the NS2/NS3 cleavage, supporting these initial, art-recognized, HCV protease-specific *cis* cleavages, paving the way for subsequent, *trans*, HCV protease-specific cleavages.

While the specification does not disclose the boundaries of a NS3 domain in a HCV polyprotein, it states that the 202-amino acid sequence of SEQ ID NO:65 is within the NS3 domain of a HCV and contributes to serine protease activity of a HCV protease. Publications of the subsequent art all agree that the catalytic triad of amino acids of the HCV serine proteases resides within the amino acid sequence of SEQ ID NO:65,² and that SEQ ID NO:65 resides in the NS3 domain of the HCV polyprotein. The specification fails to show, however, that the amino acid sequence of SEQ ID NO:65 functions as a protease, thus fails to exemplify or describe a polynucleotide encoding such a hepatitis C virus protease. This is because nothing in the specification indicates that at the time application serial No. 07/680,296 – the first to provide the disclosure common to the instant application – was filed on April 4, 1991, Applicant possessed a polynucleotide encoding a polypeptide that functions as an HCV protease by cleaving either a peptide or polypeptide HCV substrate comprising an amino sequence set forth at page 21, lines 13-15, of the specification or by cleaving any other substrate. The

² The amino acid of SEQ ID NO:65 commences at position 1006 and terminates at position 1206 of the 3011-amino acid sequence of the HCV1 polyprotein having the NCBI Accession No. GNWVC3 reported by Choo et al., made of record herewith.

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results Example 5 reports at pages 31-32 of the specification cannot be shown to have been caused by the proteolytic activity of an HCV-encoded protein, or domain, present in Applicant's particular fusion protein expressed in *E. coli* host cells because the expressed fusion polypeptide includes no peptide sequence actually recognized and cleaved by as much of the NS3 domain that the "protease", or fusion polypeptide, comprised. For the following reasons, the products detected by ELISA in Example 5 could only be produced by activity of the host cells' endogenous proteases:

A. The P600, P500, P300, or P190 fusion constructs³ of Example 4, expressed in *E. coli* host cells of Example 5, do not comprise the NS4A serine protease cofactor present at positions 1678 through 1696, inclusive,⁴ of the HCV1 polyprotein do not comprise the P6-P1' sequence of the NS3/NS4 cleavage site between HCV1 positions 1652 through position 1658, inclusive, and lack the 21 carboxyl-proximal amino acids of the NS3 domain that lie between the P600 construct C-terminus and the P6 position of the NS3/NS4 cleavage site. The NS4A cofactor peptide region adjacent to the C-terminus of the NS3 domain and contributing to the formation of the active site cleft of the NS3 domain serine protease, thus enabling both *cis*- and *trans*-cleavages,⁵ is also absent from all products expressed with the constructs of the specification's Example 4. The

³ SEQ ID NO:68, not required by a claimed method but representing the HCV1 polyprotein sequence in Applicant's fusion polypeptide encoded by the P600 construct of Example 4, comprises all of SEQ ID NO:65 and additional HCV1 amino-proximal and carboxyl-proximal sequence regions, extending from position 946 through position 1630 of the HCV1 polyprotein but excluding the 27 amino acids of the NS3 C-terminus, comprising the NS3/NS4 cleavage site, and all of the NS4 domain. The product of the P500 construct comprises SEQ ID NO:65 and excludes 197 amino acids of the NS3 C-terminus, comprising the NS3/NS4 cleavage site, and the entire NS4 domain.

⁴ Kim et al., 1996, made of record herewith. See the NS4A sequence G S V V I V G R I V L S G K P A I I P set below, and corresponding to, the chymotrypsin sequence region in the second, continuing, comparison array of Figure 5 and see discussion at pages 344-350 and Figures 1-4 and 6.

⁵ Tomei et al., 1996, made of record herewith, show in the paragraph spanning pages 1066-68, and Figures 1 and 2b, that even "*cis*-cleavage could not occur" in products expressed from constructs encoding "NS3/NS4 precursors carrying deletions in the N-terminal portion of NS4A . . . because the sequence of the NS3-NS4A junction was mutated" even though another product expressed using a construct wherein only a short sequence encoding the cleavage site peptide itself was deleted was capable of appropriately conducting *trans*-cleavage.

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subsequent art made of record herein recognizes no *cis*- or *trans*-cleavages of a HCV proteolytic activity involving the NS3/NS4 cleavage site when the sequence of the NS4A cofactor peptide is entirely unavailable.⁶ Since the NS3/NS4 cleavage site sequence is likewise absent from products expressed with constructs of the specification's Example 4, no authentic *cis* cleavage at the NS3/NS4 cleavage site can occur. Indeed, the art of record herein recognizes no HCV protease-specific cleavage site within the HCV amino acid sequence portions of Applicant's fusion polypeptides encoded by the P600, P500, P300 and P190 constructs. Thus, the specification describes no protease-encoding polynucleotides meeting its own definitions, polynucleotides comprised by compositions and expression vectors of claims 27-44 herein, supporting a conclusion that Applicant was in possession of any polynucleotide encoding a protease capable of conducting HCV NS3/NS4 *cis*-cleavage at the time the priority application was filed.

B. Similarly, the specification provides no adequate description of polynucleotides encoding HCV proteases claimed herein supporting a conclusion that Applicant was in possession of polynucleotide encoding proteases capable of conducting HCV NS2/NS3 *cis*-cleavage, or a claimed assay to detect an inhibitor of HCV NS2/NS3 *cis*-cleavage, at the time the priority application was filed. Each of the P600, P500, P300 and P190 constructs of Example 4 encode fusion polypeptides wherein the HCV region commences at position 946 of the HCV1 polyprotein, thus comprise the carboxyl-terminal 79 amino acids of the NS2 domain, the NS2/NS3 cleavage site, and at least the amino-terminal 70 amino acids of the NS3 domain in the product of the P190

⁶ Yao et al., 1999, made of record herewith, required the presence of the NS4A residues 21-32, page 1361, Materials and Methods, to form NS3 domain crystals, the structures of which, Figures 1, 2, and 4-6, demonstrate the autoproteolytic, *cis*-cleavage, interaction of the C-terminus of the NS3 domain and the first 14 amino acids of the NS4 domain in the active site cleft of the NS3-NS4 protease, Figures 2(a), 4(b) and 5, that aligns the P6 through P1' amino acids of the NS3/NS4 cleavage site. See further, Pasquo et al, 1998, made of record herewith.

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construct.⁷ Publications subsequent to the priority filing of the present disclosure establish, however, that at least the carboxyl-terminal 113 amino acids of the NS2 domain must be combined with at least the 181 amino-terminal amino acids of the NS3 domain for *cis*-cleavage.⁸ Products of Applicant's P600, P500, and P300 constructs all comprise an adequate region of the NS3 domain and the N2/N3 cleavage site sequence, but no product encoded by the constructs of Example 4 has the further forty amino acids of the NS2 domain needed for *cis*-cleavage at the NS2/NS3 cleavage. Thus host cell cleavage is the only likely explanation for the cleavages of Example 5 that Applicant argues are HCV protease-specific. Rather than suggesting that any HCV amino acid regions beyond those in the product of the P600 construct are involved in HCV protease activity, the specification teaches away from including additional HCV regions by indicating that truncating the P600 construct can establish a product having HCV-specific proteolytic activity.

Claims 29, 30, 34, 35, 39 and 40 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a new ground of rejection. Claims 29, 30, 34, 35, 39 and 40 are drawn to compositions and expression vectors comprising polynucleotides encoding genera of polypeptides comprising either of SEQ ID NOS: 63 or 64 that are active proteases but are unsupported by an adequate written description in the specification. This is because the recited structural features are not sufficient to produce a protein having proteolytic activity. The Federal Circuit has said that a sufficient written description of a

⁷ Products of the P300, P500, and P600 constructs comprise increasingly more extensive amino-proximal regions of the HCV NS3 domain beyond these amino-terminal 70 amino acids.

⁸ See Pallaoro et al, 2001, and Thibeault et al., 2001, both made of record herewith, who independently used increasing deletions of both termini of HCV NS2-NS3 region polypeptides to establish the minimal the boundaries of minimal contributions of both domains needed for *cis*-cleavage of the NS2/NS3 site between the two domains, arriving at almost identical results.

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genus of DNAs may be achieved by disclosure of a representative number of DNAs defined by their nucleotide sequences or recitations of structural features common to members of the genus, which features constitute a substantial portion of the genus. Similarly, a disclosure of a representative number of proteins defined by amino acid sequence or a recitation of structural features common to members of the genus, which features constitute genus, may constitute an adequate written description of a genus of protease-encoding polynucleotides. However, in the instant application, the structural features of the genus (i.e., comprising either of SEQ IDs NOS:63 or 64) recited in claims 29, 30, 34, 35, 39 and 40 cannot provide a basis for a substantial portion of a genus of protease-encoding polynucleotides as the remainder of the protein structure necessary for protease activity is completely undefined.⁹ The peptides of SEQ ID NOS:63 and 64 cannot in themselves have protease activity and the specification does not define the remaining structural features necessary for members of the genus of the protease-encoding polynucleotides to be selected.

Claims 27-44 are rejected, under 35 U.S.C. § 112, first paragraph, because the specification does not enable the preparation of compositions and expression vectors comprising polynucleotides encoding a hepatitis C virus protease encoded by any of the P600, P500, P300 or P190 constructs or comprising more than the HCV amino acid sequence region present in SEQ ID NO:68, or a generic version thereof, or an active truncation analog thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Applicant's arguments filed 10 January 2005 have been fully considered but they are not persuasive because disclosed structures Applicant argues are responsible for proteolysis, while necessary for HCV-specific proteolysis, have been shown to be insufficient for HCV-specific proteolysis. Applicant argues that the specification teaches

⁹ The undecapeptide of SEQ ID NO:63 extends from position 1080 through position 8109 of the HCV1 polyprotein and includes the art-accepted histidine of the catalytic triad at position 1083, while the nonapeptide of SEQ ID NO:64 extends from position 1161 through position 1169 of the HCV1 polyprotein and includes the art-accepted serine of the catalytic triad at position 1165.

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how to use at least a minimal region of "199-299" amino acids within Figure 1, where Figure 1 represents the amino acid sequence of the region of the HCV1 polyprotein encoded by the P600 construct of Example 4, to conduct claimed assays. As explained at pages 7-10 above, the amino acid sequence of Figure 1 lacks the forty amino acids of the NS2 domain amino acid sequence amino-proximal to the sequence of Figure 1 necessary for *cis*-cleavage at the NS2/NS3 junction and also lacks the sequence of the NS3/NS4 cleavage site, the 21 carboxyl-proximal amino acids of the NS3 domain that lie between the P600 construct C-terminus and the P6 position of the NS3/NS4 cleavage site, and the amino acid sequence of the P4A cofactor, necessary for *cis*-cleavage at the NS3/NS4 junction. Although the specification identifies a region in the hepatitis C virus NS3 polyprotein with sequence characteristics of a serine protease, i.e., the amino acid sequence of SEQ ID NO:65, and points to analogies between this region and proteolytic products located in similar regions of polyproteins encoded by flavivirus genomes, it provides no guidance for preparing a polynucleotide encoding an HCV-specific protease. Where specification describes no polynucleotides encoding a protease capable of cleaving either of the art-recognized NS2/NS3 and NS3/NS4 junction sequences, or other art-recognized cleavage sites in HCV polyproteins, it cannot enable the artisan seeking to determine how much of the hepatitis C virus polyprotein is sufficient to constitute a protease in order to make a protease with activity specific to a HCV protease and, indeed, teaches away from including those regions of a HCV amino acid sequence that the art recognizes are necessary for activity specific to a HCV protease, whether cleaving in *cis* or in *trans*.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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Claims 27-44 are rejected, under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments filed 10 January 2005 have been fully considered but they are persuasive only with respect to the aspect of the rejection affecting the recitation of "[a] composition comprising an isolated . . . polynucleotide". Applicant argues limitations not present in the claims where the recitation, "NS3 domain hepatitis C virus protease or an active . . . truncation analog", does not indicate how the public or one of ordinary skill in the art can determine what is meant by the term "domain" where the specification provides no specific, structural, description of the metes bounds of the NS3 domain intended or how to distinguish it from "an active truncation analog". Claims 27-44 are indefinite because claims 27, 32, and 37, from which claims 28-31, 33-36 and 38-43 depend, recite, "compris[ing] an HCV NS3 domain protease or an active . . . truncation analog", and one of ordinary skill in the art cannot tell what is meant by the term "domain" where the specification provides no specific, structural, description which domain is intended. Applicant's reference to pages 5-6 of the specification as defining an NS3 is inadequate because the flavivirus NS3 domain features discussed between lines 23-26 of page 5 are not supported by any "schematic alignment" of HCV and flavivirus amino acid sequences of Figure 1 of the specification indicated at page 5, lines 20-23, where Figure 1 depicts no alignment or comparison of the HCV amino acid sequence with another amino acid sequence. The public and the artisan attempting to establish the scope of the claimed subject matter cannot determine what is more than a "domain", thus excluded by the claim, or what is less than a "domain", yet is also a truncation analog of the claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

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(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 27-31 and 44 are rejected under 35 U.S.C. § 102(a) as being anticipated by Reyes et al., WO 90/00597, of record, for the reasons set forth at page 9 of the communication mailed 09 July 2004.

Applicant's amendment to the specification filed 10 January 2005, perfecting the claim to priority, requires that the rejection of record previously made under 35 U.S.C. § 102(b) now be stated under 35 U.S.C. § 102(a). Published on 25 January 1990, the Example 2 at page 29 of Reyes et al. anticipates claims 27-31 in disclosing the preparation of hepatitis C virus particles. This is because a composition cannot properly comprise an "isolated" polynucleotide and because a composition that comprises a polynucleotide encoding an hepatitis C virus "proteolytic polypeptide" that comprises some or all or a "NS3 domain protease" is also the hepatitis C virus particle itself.

Claims 27-31 remain rejected, and the new claim 44 is now rejected, under 35 U.S.C. § 102(a) as being anticipated by Choo et al., EP 318216, of record, for the reasons set forth at page 9 of the communication mailed 09 July 2004.

Applicant's amendment to the specification filed 10 January 2005, perfecting the claim to priority, requires that the rejection of record previously made under 35 U.S.C. § 102(b) now be stated under 35 U.S.C. § 102(a). Published on 31 May 1989, the Example IV.A.1. at pages 27-28 29 of Choo et al. anticipates claims 27-31 in disclosing the preparation of hepatitis C virus particles in a supernatant prepared from infected chimpanzee plasma, as well as the subsequent extraction of the hepatitis C virus genome from the viral particles into an aqueous composition. This is because no composition can properly comprise an "isolated" polynucleotide and a composition comprising a polynucleotide which encodes an hepatitis C virus "proteolytic polypeptide" comprising some or all or a "NS3 domain protease" is also the hepatitis C virus itself.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

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applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone number for all communications for the organization where this application or proceeding is assigned is now 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is now 571.272.1600.

William W. Moore
31 March 2005



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